REMARKS

Interview Summary

Applicants thank the Examiner for the interview of August 25, 2005. During the interview, the five remaining obviousness rejections were discussed. Applicants' representatives argued that the rejection of the pending claims under 35 U.S.C. §103, as obvious in light of various combinations of *Segre* (U.S. Patent No. 5,494,806), *Potts* (Diseases of the Parathyroid Gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's Principles of Internal Medicine, 12th Edition, pages 1902-1915), and *Sato* (WO 98/13388) was improper. Applicants' representatives stated that one of ordinary skill in the art would not have a reasonable expectation of success in using anti-PTHrP antibodies to treat hypercalcemic crisis based on the teachings of the cited references and the specification.

The Applicants' representatives discussed Example 1 of the specification with the Examiner, which demonstrates the lack of efficacy of the typical hypercalcemia treatment Elcitonin in treating hypercalcemic crisis. Administration of an anti-PTHrP antibody of the present invention, however, was effective. In contrast to the prior art compound, the antibody yielded decreased blood calcium levels in as little as 4-6 hours, and was able to maintain the decreased blood calcium levels. These results are summarized in Figures 3 (mouse hypercalcemic crisis model) and 5 (rat hypercalcemic crisis model), which are attached. After reviewing this data, the Examiner stated that the obviousness rejections could be overcome by amending the claims to reflect the percentage reduction in blood calcium level, which occurs shortly after PTHrP antibody

administration. The Examiner agreed that this treatment profile distinguished the present invention from the prior art.

Applicants have amended claims 1, 13, and 33 accordingly. Applicants have also canceled claims 34-42 and added new claims 43-53. Support for the new and amended claims can be found in the substitute specification as originally filed at, for instance, Figures 3 and 5 and the paragraph spanning pages 6 and 7, and in the application as originally filed. Therefore, no new matter has been added.

Claims 1, 4, 6, 9-16, 19-21, 33, and 43-53 are pending in this application.

Rejections under 35 U.S.C. § 103(a)

In the present Office Action, the Office makes several obviousness rejections.

1. Claims 1, 4, 9, 10, 12, 13-15, 19, 20, 33-38, 40 and 41 are rejected as being obvious over *Segre* (U.S. Patent No. 5,494,806) in view of *Potts* (Diseases of the Parathyroid Gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's Principles of Internal Medicine, 12th Edition, pages 1902-1915) and *Schlom* (In: Molecular Foundations of Oncology, Sameule Broader, Ed., 1991, pages 95-134). Office Action at 2.

2. Claims 1, 4, 9-15, 19-21, 33-38 and 40-42 are rejected as being obvious over *Segre* and *Potts* and *Schlom* and further in view of *Gristina* (U.S. Patent No. 5,681,565). Office Action at 6.

3. Claims 1, 6, 9, 10, 13, 16, 19, 20, 33-36, 39, 40 and 41 are rejected as being obvious over the abstract of *Sato* (WO 98/13388) in view of *Potts. Id.*

4. Claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20, and 33-41 are also rejected as being obvious over *Sato* and *Potts* and further in view of *Schlom.* Office Action at 8.

5. Claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20, and 33-42 are also rejected as being obvious over *Sato* and *Potts* and *Schlom* and further in view of *Gristina.* Office Action at 9.

The Office cites *Segre* for teaching a method of treating hypercalcemia comprising the administration of antagonists of PTHrP. *See* Office Action at 3. The Office states that

Sato teaches the use of humanized #23-57-137-1 monoclonal antibody to treat hypercalcemia and other disorders caused by cancer. *See* Office Action at 7. Finally, the Office cites *Potts* as teaching that the humoral mediator of malignancy associated with hypercalcemia is PTHrP and that coma and cardiac arrest can occur when serum calcium levels are at 15 to 18 mg/dl or higher. *Id.* Applicants respectfully traverse these rejections.

Applicants maintain that the Office has failed to establish a *prima facie* case of obviousness because a skilled artisan would not reasonably expect to succeed in treating hypercalcemic crisis using humanized PTHrP antibodies if he were to combine the references cited by the Office. While *Segre*, *Potts*, and *Sato* discuss the treatment of hypercalcemia, there are many shortcomings associated with the use of prior art treatments for hypercalcemia in the treatment of hypercalcemic crisis. It was therefore surprising that humanized PTHrP antibodies of the invention were able to effectively treat hypercalcemic crisis, by decreasing the blood calcium level in a short period of time and maintaining the decrease, for instance.

The specification illustrates that it was well recognized that traditional treatments for hypercalcemia did not effectively treat hypercalcemic crisis. The need for drugs having higher therapeutic effects and fewer side effects exists because traditional hypercalcemia treatments "have such disadvantages that therapeutic effects may be depressed when successively administered, that severe adverse side effects may be produced, and that the development of pharmacological effects may be delayed." Substitute specification, page 3, lines 10-19. While these agents may be effective in

treating hypercalcemia, the problems associated with their use in treating hypercalcemic crisis are many. The *Potts* reference cited by the Office also acknowledges the shortcomings of hypercalcemia agents for the treatment of hypercalcemic crisis. For instance, *Potts* states that "[i]ntravenous phosphate is one of the most dramatically effective treatments available for severe hypercalemia but is toxic and even dangerous so that it is used rarely." *Potts*, page 1914, left column.

The lack of efficacy of typical hypercalcemia treatments is demonstrated in Example 1 of the Specification. Using hypercalcemic crisis model animals (human tumor-transplanted mice and rats), a humanized antibody against PTHrP as well as a prior art calcitonin preparation were examined for their therapeutic efficacy. *See* substitute specification, Example 1, pages 24-28. Calcium levels were basically unchanged in both mice and rats treated with Elcitonin (a calcitonin preparation) and untreated rats after 24 hours. *See* substitute specification, page 27; figures 3 and 5. The humanized PTHrP antibody of the invention, however, is able to reduce blood calcium level and maintain the decrease 24 hours after administration. *Id.* Thus, administration of compositions of the present invention are able to continuously and effectively suppress calcium levels when calcium rapidly increases to severe levels during hypercalcemic crisis, and can be rapidly effective, yielding results in as little as 4-6 hours.

The *Sato*, *Segre*, and *Potts* references provided by the Office discuss the use of various agents in the treatment of hypercalcemia. However, these references provide no reasonable expectation that the agents would be similarly effective in the treatment

of hypercalcemic crisis. Data provided in the specification and the cited references demonstrate that prior art agents are unable to effectively treat hypercalcemic crisis. Yet surprisingly the humanized antibody of the present invention is able to rapidly decrease and maintain blood calcium level.

In addition to *Sato*, *Segre*, and *Potts*, the Office cites *Schlom* (teaching the use of antibody fragments for maximum penetration into the tumor vasculature), and *Gristina* (teaching PEG as an antibody carrier) as support for the obviousness rejection. *Schlom* and *Gristina*, however, do not cure the defects described above, as they do not teach or suggest the use of humanized PTHrP antibodies to treat hypercalcemic crisis. Based upon the difficulties described above and the Applicants unexpected success, Applicants respectfully submit that the present invention is nonobvious.

The Office stated that the ability of humanized PTHrP antibodies to quickly decrease the severe blood calcium levels of hypercalcemic crisis was nonobvious. *See* Interview Summary, *supra*. Thus, Applicants have amended claims 1, 13, and 33 to reflect such a decrease after administration of an anti-PTHrP antibody. Applicants reserve the right to pursue the other claim embodiments in a separate application. Applicants also canceled claims 34-42, which would replicate the claims as amended, and added new dependent claims 43-53. In light of these claim amendments, Applicants respectfully request the Office to withdraw the obviousness rejections of the pending claims.

Obviousness-Type Double Patenting Rejections

The Office provisionally rejected claims 1, 4, 6-16, 19-21 and 33 under the doctrine of obviousness-type double patenting, stating that these claims are not patentably distinct over claims 126-136 and 138 of copending Application No. 09/269,332 in view of *Potts* and *Schlom*. Office Action at 10. Further, the Office provisionally rejected claims 1, 4, 6-16, 19-21 and 33 under the doctrine of obviousness-type double patenting, stating that the claims are not patentably distinct over claims 126-136 and 138 of copending Application No. 09/269,332 and *Potts* and *Schlom* and in further view of *Gristina.* Office Action at 11.

Applicants respectfully traverse these rejections, based on the arguments outlined above. Briefly, Application No. 09/269,332, *Segre*, and *Potts* references provided by the Office discuss the use of various agents in the treatment of hypercalcemia. However, these references provide no reasonable expectation that the agents would be similarly effective in the treatment of hypercalcemic crisis. Data provided in the specification and the cited references demonstrate that prior art agents are unable to effectively treat hypercalcemic crisis. Yet surprisingly the humanized antibody of the present invention is able to rapidly decrease and maintain blood calcium level. Furthermore, *Gristina* does not cure these defects. In light these arguments and the claim amendments made by the Applicants, Applicants respectfully request the Office to withdraw the obviousness-type double patenting rejections of claims 1, 4, 6-16, 19-21 and 33.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Attachments: Figures 3 and 5